REMARKS

Upon entry of the proposed amendment, claims 1-5, 18-23, 46, 49-50, 61, 69-71 and 93-106 are pending.

35 U.S.C. § 112, first paragraph

Claims 46 and 93-106 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled. Significantly, however, a claimed invention is enabled under the patent laws unless the Examiner comes forth with evidence or technical reasoning indicating some reason to doubt the truth of the statements made in the patent application. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); MPEP § 2164.04. The Office Action points to no evidence indicating that those skilled in the art would doubt that the compounds of the invention will exhibit at least some patentable utility.

Applicants have actually demonstrated that compounds falling within the scope of the claim have activity as antagonists of endothelin and angiotensin II receptors. The MPEP states that "data generated using *in vitro* assays . . . almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound. *See*, MPEP § 2107.03.

Additionally, it is well known in the art that the endogenous peptides angiotensin II and endothelin are powerful vasoconstrictors and mitogens, and both peptides have been implicated in the pathogenesis of hypertension and cardiovascular disease. *See, e.g.*, Yanagisawa *et al.*, "A novel potent vasoconstrictor peptide produced by vascular endothelial cells," *Nature (London).* **1988**, *332*, 411-15; Inoue, *et al.*, "The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes," *Proc. Natl. Acad. Sci. U. S. A.* **1989**, *86*, 2863-7; Ferrario, "The Renin-Angiotensin System: Importance in Physiology and Pathology," *J. Cardiovasc. Pharmacol.* **1990**, *15* (Suppl. 3), S1-S5; and Wexler, *et al.*, "Nonpeptide Angiotensin II Receptor Antagonists: The next Generation in Antihypertensive Therapy," *J. Med. Chem.* **1996**, *39*, 625-656. *In fact, there are drugs currently on the market for treating endothelin-dependent and angiotensin II-dependent disorders.* For example, bosentan, an endothelin antagonist, is on the market for the treatment of hypertension;

irbesartan and losartan, both of which are antagonists of angiotensin II, are FDA-approved anti-hypertensive drugs.

Moreover, it is art recognized that elevated levels of angiotensin II promote the synthesis and vasoconstrictive action of endothelin, and elevated levels of endothelin increase the synthesis vasoconstrictive action of angiotensin II, thus creating a positive dual feedback mechanism and an excellent target for treating hypertension. *See, e.g.,* Imai *et al.*, "Induction of endothelin-1 gene by angiotensin and vasopressin in endothelial cells," *Hypertension.* **1992**, *19*, 753-757; Chua, *et al.*, Regulation of endothelin-1 mRNA by angiotensin II in rat heart endothelial cells," *Biochim Biophys Acta.* **1993**, *1178*, 201-206. A considerable body of preclinical evidence has shown that simultaneous antagonism of both the angiotensin system and the endothelin system can produce a greater reduction in blood pressure and added cardiovascular benefit than antagonizing either system alone.

For example, in a canine model of renovascular hypertension, the combination of an angiotensin II receptor antagonist (losartan) with an endothelin antagonist (bosentan) produced a 40 mm Hg reduction in mean blood pressure, compared to a 20 mm Hg decrease with losartan alone. *See*, Massart, *et al.*, "Angiotensin II and endothelin-1 receptor antagonists have cumulative hypertensive effects in canine Page hypertension," *J. Hypertension* **1998**, *16*, 835-41.

In another study, using a rat model of hypertension and heart failure, the combination of losartan with an endothelin receptor antagonist (LU-135252) worked synergistically to return blood pressure, heart weight and mortality levels to those of the non-hypertensive controls. *See*, Bohlender, *et al.*, "Synergistic effects of AT1 and ETA receptor blockade in a transgenic, angiotensin II-dependent, rat model," *Hypertension* **2000**, *35*(4), 992-997.

Similar synergistic benefits of dual Angiotensin II and endothelin receptor antagonism have been demonstrated in several other animal models of hypertension such as in DOCA-salt rats, in spontaneously hypertensive rats (SHRs) and in diabetic rats. *See*, Gardiner, *et al.*, "Hemodynamic effects of losartan and the endothelin antagonist, SB 209670, in conscious, transgenic ((mRen-2)27), hypertensive rats" *Br. J. Pharmacol.* **1995**, *116*, 2237-44; Dhein, *et al.*, "Long-term effects of the endothelinA receptor

antagonist LU 135252 and the angiotensin-converting enzyme inhibitor trandolapril on diabetic angiopathy and nephropathy in a chronic type I diabetes mellitus rat model," *Journal of Pharmacology and Experimental Therapeutics* **2000**, *293*(2), 351-359; Ikeda, et al., "Antihypertensive effects of a mixed endothelin-A- and -B- receptor antagonists, J-104132, were augment in the presence of a AT1-receptor antagonist, MK-954," *J Cardiovasc Pharmacol.* **2000**, *36*, S337-S341.

In view of the forgoing remarks, and in the absence of evidence indicating that the claimed compounds would not work for their intended purpose, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph rejection.

35 U.S.C. § 112, second paragraph

Claims 1-5, 18-23, 46, 49, 50, 61, 69-71 and 93-106 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

The Examiner states that the terms "heteroaryl" and "heterocycloalkyl" are indefinite because the size of the ring and the types of heteroatoms are not defined. However, both "heteroaryl" and "heterocyclo" are clearly defined in the specification, including the ring size and types of heteroatoms. *See* pages 13-14 of the specification. The term "heterocycloalkyl," just like the term "arylalkyl," simply refers to a "heterocyclo" connected through an "alkyl." Thus, Applicants request withdrawal of this rejection.

The Examiner also states that the terms "enantiomers, diasteremoers and solvates" are indefinite and "[t]here is not even a single example present in the specification for preparing specific enantiomers, diastereomers or solvates." Applicants respectfully submit that Examples 25-26, 124-147, 161-166, and 169-172 in the specification are all specific examples of enantiomers of the compound of formula I. In addition, an ordinary skilled in the art would know how to make enantiomers, diastereomers or solvates (in particular, hydrates) of the compound of formula I based on the disclosure of the present application. Accordingly, Applicants request withdrawal of this rejection.

The Examiner further requests a clarification of the last paragraph in claim 1. Since Applicants have amended claim 1 to define which rings may be optionally substituted, and therefore, a withdrawal of the rejection is also requested.

Finally, the Examiner states that endothelin-dependent or angiotensin II-dependent disorders are not defined. However, as discussed above, endothelin-dependent or angiotensin II-dependent disorders are well known in the art. Furthermore, the utility section of the instant application clearly describes that the compounds of formula I are antagonists of both endothelin and angiothesin II receptors, and therefore are useful, among other things, as antihypertensive agents. *See* pages 51-61 of the specification. Applicants thus respectfully request a withdrawal of this rejection.

In view of the amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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